HIGHLIGHTS

- The use of drug eluting stents is gaining ground in interventional cardiology
- In this sense, a comparative assessment of available agents is imperative, for informed decision making
- A mixed treatment comparison was utilised to compare bare metal, 1st and 2nd generation drug eluting stents
- We assessed stents on terms of Target Vessel Revascularization, Thrombosis, Myocardial Infarction and Cardiac death
- Everolimus, resolute and biolimus carry the highest probabilities of being superior for all endpoints.

TITLE PAGE

A mixed treatment comparison for short- and long-term outcomes of bare metal and drug eluting coronary stents

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Abstract

Background The increasing use of drug eluting stents in interventional cardiology calls for assessment of their efficacy and safety, both among drug eluting and bare-metal stents , in the context of rational decision making.

Methods We searched for papers that compared any of the sirolimus eluting stents, paclitaxel eluting stents, drug eluting stent , biodegradable stent, everolimus eluting stents, zotarolimus resolute eluting stent, biolimus eluting stent, bare metal Stent and zotarolimus eluting stents. The search was contacted through Medline, the Cochrane database, Embase, TCTMD, ClinicalTrials.gov, Clinical Trial Results, CardioSource, abstracts and presentations from major cardiovascular meetings. We also searched for further articles cited by selected papers. Further, important conferences and relevant proceedings and abstracts, such as the American Heart Association, American College of Cardiology, Transcatheter Cardiovascular Therapeutics, Society of Cardiovascular Angiography and Intervention, European Society of Cardiology, and Euro-PCR, were also searched. Inclusion criteria were : Randomised Controlled Trials (RCT), size of study (≥ 100 patients), duration more than 6 months and definition of reported endpoints (Target Vessel Revascularization, Thrombosis, Myocardial Infarction and Cardiac death). Analysis of the data was performed for short term (less than a year) and long term(more than a year). A mixed treatment comparison approach was utilized for the data analysis.

Conclusions

Based on the rankings of each treatment, a distinct difference between 2nd and 1st generation stents was identified . We can conclude that everolimus, resolute and biolimus carry the highest probabilities of being superior for all endpoints.

HIGHLIGHTS

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1. Introduction

The introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977 marked a new era in operational cardiology. A landmark year for operational cardiology was 1986, during which the introduction of the first stent in clinical practice by Puel and Sigwart [1], led to a fast uptake of this new technology . By 1999, stenting composed 84.2% of all Percutaneous Coronary Interventions (PCI) performed[2] .

Although Bare Metal Stents (BMS) demonstrated a clear benefit, by reducing occurrence of acute mechanical complication of angioplasty and restenosis rates[3], stent thrombosis and late term restenosis still emerged as major challenges [4]. Neointimal hyperplasia, which on a cellular level is a reactive excessive growth of tissue around the stent, is exacerbated by BMS. Along with optimization of antiplatelet therapy and introduction of more potent agents, Drug Eluting Stents (DES) were developed in order to tackle the cellular reaction, by the sustained release of an antiproliferative (cytotoxic or cytostatic) substance from their surface, in order to limit cell growth. In 2003, sirolimus and paclitaxel eluting stents were introduced to clinical practice, demonstrating reduced need for revascularization and reduced angiographic late lumen loss compared to BMS[5], without proving significant superiority in mortality and myocardial infarction rates[6].However, the most alarming finding was their relation to an increased late thrombosis rate[7-10]. Formation of atheromatic plagues may occur earlier, and more frequently, with drug-eluting compared to bare-metal stents, [11] resulting in high rates of early and late stent thrombosis after discontinuation of dual antiplatelet therapy, thus leading to ongoing susceptibility for thrombosis after the first

year. Moreover, inflammation of the arterial wall, poor endothelisazation and delayed healing aggravated the risk for late thrombosis [12].

Capitalizing on the significant superior effect of first generation DES on target vessel revascularisation (TVR) [13], a new (second generation) category of DES with innovative materials and antiproliferative agents were developed to cope with this issue. Second generation DES have been established as the cornerstone in PCI in patients presenting with coronary artery disease[14]. The majority of these agents were approved in non inferiority trials, compared to first generation DES or BMS[15].

Evidence based decision making in health requires the use of high quality Randomized Controlled Trials (RCT) that compare directly two (2) or more interventions and are undoubtly the cornerstone of informed decision making in health [16]. Nevertheless, the design of RCT is usually compared either to a placebo or an obsolete technology. Rarely does an RCT include all potential comparative products, primarily due to the high cost incurred, the regulatory impediments, as well as strategic decisions

This creates a gap in the assessment process, which can be bridged with pioneering statistical methods, thus enabling the comparison of different treatments which form a connected treatment network but may not have been directly compared in trials [17-18]. In light of the above, we compare the safety and effectiveness profile between drug eluting stents and bare stents, using Mixed Treatment Comparisons (MTC, also known as network meta-analysis or multiple treatment meta-analysis). MTC contribute further to the body of evidence by estimating the relative effects for treatments not directly compared, and by pooling both direct and indirect evidence, where available,

to strengthen inferences. MTC are an extension of the standard (two-treatment) meta-analysis to comparisons of more than two treatments forming a connected network of evidence (such as eg Fig 1), where all treatments and studies included are relevant to the decision[17-19].

The current paper adheres to ISPOR-AMCP-NPC Good Practice Task Force Report for Indirect Treatment Comparison/Network Meta-Analysis Studies[20].

We included 6 DES, 5 coated with mammalian Target of Rapamycin Inhibitors as coating agent – Zotarolimus, Everolimus, Sirolimus, Biolimus and zotarolimus resolute – and one antimitotic agent, paclitaxel. This study advances further literature, since previous reports did not include comparisons between *all* commercially available stents [21-22], including BMS.

2. Literature review

We adopted the PRIMA [23] (Preferred Reporting Items for Systematic Reviews and Meta- Analyses) statement for reporting systematic reviews and metanalysis in healthcare. We used the MESH terms:“drug eluting stent”, “bare metal Stent”, and also the INN of the drug used in the durable polymer stent (“sirolimus eluting stents”, “paclitaxel eluting stents”, “drug eluting stent” , “Endeavor zotarolimus stent”, “ biodegradable stent”

“everolimus eluting stents”, “zotarolimus resolute etuling stent”, “biolimus eluting stent” and “zotarolimus eluting stents”). The search lasted until the end of May, 2013.

We searched Medline, the Cochrane database, Embase, TCTMD, ClinicalTrials.gov, Clinical Trial Results, CardioSource, abstracts and presentations from major cardiovascular meetings. We also searched for

further articles cited by selected papers. Further, important conferences and relevant proceedings and abstracts, such as the American Heart Association, American College of Cardiology, Transcatheter Cardiovascular Therapeutics, Society of Cardiovascular Angiography and

Intervention, European Society of Cardiology, and Euro-PCR, were also searched.

Lastly, we contacted authors, in cases of unclear data or in cases where clarification on study design was required.

2.1. Selection of data

Two (2) researchers (P.P and M.T.) independently critically assessed selected papers and there was a crossover of assessment: Any disagreements were resolved by consensus. Authors and manufacturers were contacted in case of discrepancy. 64 trials were included for short term studies and 42 for long term studies (table 1).

Table 1.

We used GRADE [24] criteria for assessment of evidence and also the Cochrane collaboration bias [25] tool. We defined several criteria for trial inclusion criteria as following:

- Randomised Controlled Trials (RCT).
- Size of study (≥ 100 patients)
- Duration more than 6 months.
- Definition of reported endpoints (TVR, THROMBOSIS, MI and Cardiac death)

2.2. Data extraction

Due to several concerns regarding the short and long term safety of stents, along with a clear division of short and long term effects of stents, we created 2 sub-analysis: Long-term (more than a year) and short term (less than a year- including studies that lasted 1 year). Endpoints were divided into efficacy and safety outcomes. The efficacy outcome was target-vessel revascularization (TVR) and the safety outcomes were cardiac death, myocardial infarction (MI),which includes fatal and non-fatal non-Q-wave or Q-wave myocardial infarction, and stent thrombosis. Stent thrombosis was evaluated according to the Academic Research Consortium (ARC) criteria [26] and we included definite, possible, and probable and secondary thrombosis as well (i.e. after a repeated TVR).

3. Statistical Methods

We used mixed treatment comparison (MTC) methods to create a comparative efficacy network of treatments which are relevant for medical decisions. This approach has two major advantages:

- It allows estimation of relative treatment effects among products not clinically tested against each other, without breaking randomisation.
- Inclusion of direct and indirect comparisons can reduce uncertainly and is the most efficient use of all relevant evidence.

A MTC meta-analysis was conducted to simultaneously compare the 7 stents. The model used assumes the number of events (Cardiac Death, Thrombosis, TVR or MI), out of the total number of patients in each arm of each included

trial follows a binomial likelihood with a certain probability of event which is modelled on the logit scale.[19]

Relative treatment effects are reported as posterior median odds ratios (OR) and 95% Credible Intervals (CrI). We also present the probability of each treatment being ranked as 1^{st}, 2^{nd}, 3^{rd}, etc. most effective for each outcome. The models were implemented using the freely available software Winbugs, version 1.4.3 [27] with code modified from Dias et al [28].

Both fixed and random effect models (where sufficient data was available) accounting for the correlations induced between trial-specific effects in multi-arm trials were considered on the basis of model fit. Studies with zero or 100% events in all arms were excluded from the analysis, because these studies provide no evidence on relative effects.

Goodness of fit was measured using the posterior mean of the residual deviance, the degree of between study heterogeneity, and the Deviance Information Criterion (DIC). In a well-fitting model the posterior mean residual deviance should be close to the number of data points.[19,29] Heterogeneity was reported as the posterior median between trial standard deviation with its 95% Credible Interval. Differences of ≥5 points for residual deviance and DIC were considered meaningful. Model fit was further assessed by inspecting individual data points' contributions to the residual deviance[19].

For the selected model (fixed or random effects), inconsistency was assessed using the node-split method [30] implemented in R [31] through the gemtc package[32]. Comparisons of the direct and indirect evidence were made, and the probability of a difference quantified through a Bayesian p-value. The P-values need to be interpreted with caution given the multiple direct vs indirect

comparisons being carried out, and the direction and strength of direct and indirect evidence as well as model fit and between-study heterogeneity were also examined to determine whether there was evidence of inconsistency [30]

3.1. Priors

We used vague normal priors with mean zero and variance 10,000 for all trial baselines and relative effect parameters. In random effects models, the between-study heterogeneity was given a minimally informative prior, Uniform between zero and five.

Model convergence was assessed through visual inspection of trace plots and through Brooks-Gelman-Rubin plots. Convergence was achieved after 40,000 burn-in iterations and we conducted at least a further 80,000 iterations (on three chains) to ensure stability and accuracy of results.

4. Results

In total the MTC analyses included 106 trials: 42 reporting long term outcomes with 48375 enrolees and 64 reporting short term outcomes with 56709 enrolees. Treatment networks for each outcome are presented in Figure 1 where the width of the edges is proportional to the number of studies making that comparison and the size of the bubbles is proportional to the number of patients randomised to that treatment.

FIGURE 1

4.1. Model choice

The Random Effects (RE) model was preferred for short term TVR, and the Fixed Effects (FE) model was preferred for thrombosis, MI and cardiac death for short term outcomes. In the long term assessment, the FE model was

preferred for cardiac death and TVR, and the RE was chosen for MI and thrombosis.

4.2. Target Vessel Revascularisation

All DES included in our analysis reduced TVR compared to BMS, and all have demonstrated effectiveness both in long and short term with 95% credible intervals that exclude “no effect”.

Long term: In the long term biolimus carries the highest probability (60%) of being the best agent, everolimus carries a 28.5% and Zotarolimus a 10% (table 2). Odds ratio between everolimus and biolimus is 1.08 (95%Credible Interval, CrI: 0.72-1.56)(table3).

Short Term : Regarding short term TVR effectiveness, everolimus is the 3rd most potent agent, resolute zotarolimus carries a 70% probability of being the most effective, and biolimus 10% (table 4). The odds ratio of resolute zotarolimus compared to biolimus is 0.79 (CI:0.39-1.42) and of everolimus compared to resolute is 0.83 (0.46-1.35) (table 5).

4.3. Thrombosis

Long term: In the long term, results suggest that everolimus may be superior to BMS (table 3). Everolimus appears to be the safest stent, although with only a 27% probability of being the best, while resolute zotarolimus and biolimus demonstrate comparative probability of being the safest stent (25% and 24.5%, respectively) (table 2).

Short Term : In the short term everolimus is superior to BMS, paclitaxel and sirolimus (table 5). Everolimus carries a dominating probability of being the

most potent in reducing the probability of thrombosis (81%) whilst resolute is the second with a much smaller probability (12%)(table 4).

4.4. Cardiac Death

For cardiac death, another safety endpoint, there were no differences among agents in the short and in the long term (tables 3,5).

Long term: Zotarolimus resolute appears to be the more potent, with a 47% probability of being the best in the long term(table 2) whilst Biolimus has 18.7% probability of being the best stent.

Short Term : Zotarolimus resolute also carries the highest probability (66 %) of being the best in the short term (table 4).

TABLE 2

TABLE 3

TABLE 4

TABLE 5

4.5. Myocardial Infarction

MI which includes fatal and non-fatal non-Q-wave or Q-wave myocardial infarction.

Short Term:

Everolimus, zotarolimus, resolute and sirolimus demonstrate short term statistically significantly potency compared to BMS (odds ratio BMS-Sirolimus 0.74 CI: 0.6-0.90, BMS –everolimus 0.62 CI: 0.48-0.79, BMS: zotarolimus 0.75 CI: 0.54-0.96, BMS-resolute 0.63 CI:0.45-0.85), while biolimus

demonstrated a trend to statistically significant CI: 0.58-1.04. (table 5). Zotarolimus resolute demonstrated the highest probability of being the most potent (46%) while everolimus ranks second (39%) (table 4). Although superiority remains in the long term as well, results are not statistically significant except the borderline superiority of zotarolimus to paclitaxel (odds ratio CI:0.55-0.99)(table 4). Nevertheless, biolimus has a 45 % of being the best, with zotarolimus second 22% and resolute third with 13 % (table 2)(Figure 2).

FIGURE 2

4.6. Inconsistency Checks

Results of inconsistency checks are presented in Appendix 1.

For TVR short term there was some evidence of disagreement between direct and indirect evidence in the comparison of everolimus with resolute zotarolimus. The P-value for inconsistency was 0.03, with direct evidence suggesting no effect whilst indirect evidence favoured zotarolimus resolute (Appendix 1).

For MI short term there was some evidence of disagreement between direct and indirect evidence for the comparison of biolimus with sirolimus, with direct evidence favouring sirolimus whilst indirect evidence showed no effect (P-value=0.02). No meaningful disagreement was identified for thrombosis or cardiac death in the short term analyses.

For the long term inconsistency check, no meaningful disagreement was identified for the TVR or cardiac death. For MI we identified possible disagreement between direct and indirect evidence for comparisons of treatments sirolimus with biolimus and everolimus with biolimus. These two

contrasts are both involved in the loop (sirolimus, everolimus, biolimus) and P-value for agreement of direct and indirect evidence is 0.03 in both cases – indicating some inconsistency. For thrombosis there was some evidence of inconsistency in the comparison of Paclitaxel with everolimus with direct evidence suggesting a large effect favouring everolimus.

5. Discussion

85% of all inserted stents in Cyprus are DES, an approach similar to other countries[33]. Therefore, assessing safety and effectiveness of stents, apart from a health issue, will have a significant impact on relevant budgets [34].

In recently published meta-analyses of randomized controlled trials (RCTs) comparing BMS to DES, DES reduce restenoses and the need for revascularization procedures, but not overall mortality or the incidence of myocardial infarction [21-22]. In our MTC, we examined the safety and the efficacy of BMS, first and second generation DES, including biodegrabale and durable polymer stent.

We can conclude that there is a notable variability among safety and effectiveness of DES. Even among second generation DES, there does not appear to be a class effect. Our analyses suggest that Everolimus is the safest, which is in line with other findings [21-22].

The Thrombosis mechanism associated with DES is a complex process and the Polymer coating of DES may aggravate thrombogenivity compared to BMS [35]. Thrombosis, as a significant safety endpoint, has been amidst a longstanding area of controversy.

Everolimus demonstrated superior safety, which can also be attributed to its biodegradable polymer. In our analysis, thrombosis rates tend to favour

second generation stents, as compared to both first generation and BMS. Thrombosis still remains a multifactorial issue with many variables, including the kinetics of drug release, the type of polymer, and strut thickness, have an impact on thrombosis rates. The FDA responded to these concerns by amending the guidelines related to antiplatelet duration in patients after stent placement [36]. Still, the optimal use of antiplatelet therapy is not defined, and thrombosis with DES, as well BMS, remain an adverse event that may occur. In the era of BMS stents, thrombosis after the first month was very rare [37]. Several authors highlight the long term risk for thrombosis with DES[38]. The addition of antiproliferative agent interacts between the coagulation process and the stent[39]. As a result, rapamycin inhibition of the mammalian target of rapamycin increases both the thrombin- and tumor necrosis factor-α–induced endothelial tissue factor expression [40]. Consequently, many authors [41-42] underline the need for longer use of antiplatelet therapy, which increases both cost and risk for adverse events.

Biolimus, proved to be the most potent, with regards to TVR reduction in the long term, however, other meta-analyses did not include it[20-21]. All DES were superior to BMS in reducing TVR, but there is variability in the size of the effect, Zotarolimus is the only second generation DES that did not demonstrate superiority compared to BMS and 1st generation stents. Nevertheless, since resolute zotarolimus was superior to BMS, this difference may be due to the release curve of the resolute zotarolimus, which further substantiates the hypothesis that other variables , beyond eluting stent, may influence the outcome.

From a health policy perspective, the hardest challenge is the combination and ranking of all four endpoints, especially TVR risk against thrombosis. TVR has a prevalence of 15% of patients involved in the analysis. In the majority of cases, it is angiographically driven by strict study protocol, without clinical symptoms, and consequently, associated with a low risk of death. On the other hand, even though thrombosis is rare, it is related to a 90% risk of death or MI [43]. Stone et al reported incidence rates for target lesion revascularization of 7.8% with SES vs 23.6% with BMS ($p < 0.001$) and 10.1% with PES vs 20.0% with BMS ($p < 0.001$) after a four year study[44]. The corresponding rates for thrombosis were only 1.2% with SES versus 0.6 with BMS ($p = 0.20$) and 1.3% with PES versus 0.9% with BMS ($p = 0.30$)[44].

Other authors did not find a statistically significant difference in primary safety endpoints (MI and death) between DES and BMS, which was another finding of our study. Nevertheless, DES were proved to be superior to BMS, with biolimus and resolute being the most potent in reducing MI and cardiac death rates.

Overall, our findings indicate that DES and BMS demonstrated similar rates of cardiac death and MI. DES are also statistically superior in TVR reduction compared to BMS, while biolimus and everolimus are superior compared to other stents. Moreover, DES are not associated with an increased rate of thrombosis. DAPT (antiplatelet therapeutic regime of aspirin plus platelet $P2Y_{12}$ receptor blocker) offers significant benefit in preventing stent thrombosis. Without DAPT, the period of high risk for stent thrombosis is longer with DES than BMS, due to a delay in neointimal coverage. Therefore, bare-metal stents are often used in patients with a history of bleeding, needing early non-

cardiac surgery, requiring anticoagulation in addition to dual antiplatelet therapy, or those who are non-compliant with their treatments.

We also point out that adoption of DES has exceeded the clinical evidence, mainly due to their high and early uptake and the off-label use. Relief of symptoms and a desire to avoid extensive procedures may be the most important factors to patients. Moreover, the concurrent angiography and placement of stents seems rational for many patients. There is a perception among patients that PCI prevents heart attacks[45], while several authors underline that stenting was the only therapeutic option offered to patients Stent implantation has become the cornerstone therapeutic approach in coronary artery disease[46] while CABG rates are declining worldwide. Although the scope of this report is to compare DES with BMS, we deem fit to comment on CABG. CABG, which denotes the surgically bypass of blocked arteries by using grafts from internal mammary arteries or saphenous arteries, is the benchmark procedure in cases such as failed PCI and significant left main coronary disease. CABG has demonstrated increased life expectancy in multi vessel disease and diffused diseases; however, the benefit is long term (after 5 years)[47] and comes along with certain risks, such as increased recovery period and susceptibility to infections. Utilisation of stents, is steadily increasing in stable patients with Coronary disease [48]. Along with stent evolution, medical therapy has also improved dramatically over this period. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, compared an initial strategy of aggressive medical therapy versus PCI with BMS in patients with stable CAD and found no statistically significant survival difference, although greater symptom relief

was associated with PCI[49] .Thus, the decision to perform a PCI in patients with stable angina is based on its effectiveness in relieving symptoms, preventing recurrent angina, and reducing repeat procedure.

Therefore, stents - both DES and BMS- must also be assessed in the broader context with other available interventions, both pharmaceutical and medical.

An implication of using MTCs is that, unlike the process for regulatory approval, the results of one company´s trial may influence the estimated relative effectiveness of another company´s product, even in cases where the other product is not used as a trial comparator.

6. Conclusion

Taking everything into account, the MTC method is a particularly important methodological development in technology appraisal because it potentially offers a potent answer to synthesis, in contexts where individual or pair-wise meta-analyses of trials do not provide coherent estimates of all the effectiveness parameters, as is often required to inform associated economic decision models. MTC methods are perhaps the most important development in evidence synthesis in recent years and their potential for use in technology assessment is considerable.

This MTC provides one of the most comprehensive comparisons in DES and BMS, including 56709 patients in the short term analysis, plus 48375 patients in the long term.

Based on the rankings of each treatment, a distinct difference between 2nd and 1st generation stents was identified . We can conclude that everolimus, resolute and biolimus carry the highest probabilities of being superior for all endpoints.

Table 6

Study	Year	Comparative Arms	Sex	Age
BASKET [50]	2005	SES (n=264), PES (n=281), BMS (n=281)	Male (79%) Male (79%)	Age (years) 64±11 Age (years) 64±12
CATOS[51]	2012	ZES (n=80) SES (n=80),	Male (65%) Male (76%)	Age (years) 62.7±12.3 Age (years) 63.0±11.7
C-SIRIUS[52]	2004	SES(n = 50), BMS(n =50)	Male (70 %) Male (68%)	Age (years) 60.3 ±10.6, Age (years) 60.7± 9.1,
CHEVALIER [53]	2007	BES (n=85),PES (n=35)	Male (69 %) Male (66%)	Age (years) 65±11, Age (years) 63±11
COMFORTABLE AMI[54]	2012	BES (n = 575) BMS(n = 582),	Male (80.5%), Male (78.2%)	Age ,(years) 60.7± 11.6, Age, (years), 60.4 ± 11.9
COMPARE [55]	2010	EES(n=897), PES (n=903)	Male (69%), Male (72%)	Age (years)62.9 ± 15.7,Age (years) 63.6±17.2
COMPARE II[56]	2013	BES(n=1795) EES(n=912)	Male (74. 4%), Male(74.3%)	Age (years) 63± 11.1, Age (years) 62.7± 11.0
DEBATER[57]	2 0 1 2	SES (n =424) BMS (n = 446 Abciximab(n = 439) , No Abciximab (n = 434)	Male (78%), Male (75%), Male (76%) Male (78%)	Age(years) 60±11 Age (years) 61±11 Age (years) 60±10 , Age, (years)60±12
DESSERT[58]	2008	SES(n = 75) BMS (n = 75)	Male(63%), Malen(49%)	Age (years) 71 ±9 Age (years) 69±9,
DIABEDES[59]	2007	SES(n = 76) PES(n =77)	Male (84%) Male (74%),	Age (years) 66 ±8, Age (years) 65 ±10
DIABETES[60]	2005	SES (n = 80) BMS (n = 80)	Male (70%) Male (81%)	Age (years) 65.9±9 6 Age (years) 7.2±10
DIAS DE LA LIERA[61]	2007	BMS (n = 54), SES (n = 60)	Male (78.3%) , Male (80.0)	Age, (years) 65 ±13 64
DIBRA[62]	2005	BMS(N=125), SES(N=125),	Male (64%), Male (68%)	Age (years) 68.3±9.6 Age (years) 67.7±10.2
E-SIRIUS[63]	2003	SES (n=175), BMS (n=177),	Men (70%), Men 126	Age (years) 62·0 ±11·4, age (years)62·6±10·3,

			(71%),	
ENDEAVOR II[64]	2006	EES(n=598), BMS (n=599)	Male (77%), Male (75%)	Age(years)61.6±10.5, Age (years) ,61.9±10.5
ENDEAVOR III[65]	2006	ZES(n=323), SES (n=113)	Male (65.3 %) Male (81.4 %)	Age (years) 61.42 ±10.58, Age (years) 61.73 ±11.59
ENDEAVOR IV [66]	2010	ZES (n =773) PES (n =775),	Men (66.9%) Men (68.5%)	Age, (years) 63.5± 11.1 Age(years)63.6 ± 11.0
ESSENCE DIABETES[67]	2013	EES(n=149) SES(n=151)	Men (52.3%) ,Men (65.6%)	Age (years) 63.2±8.3, Age (years)63.5±8.1
EXCELLENT[68]	2011	EES (n = 1,079), SES (n = 364)	Male (65.2%) Male (62.6%)	Age (years) 62.5 ±10.1 Age (years) 63.4 ±9.9
Erglis[69]	2007	BMS (n =50)), PES (n = 53)	Male (82%) Male (85%)	Age (years) 62.56 ±11.45, Age(years) 61.08± 10.28,
HORIZON AMI STONE [70]	2009	PES(N = 2257) BMS (N = 749)	Male . (77.0%), Male (76.0%)	Age (years) 59.9 Age (years) 59.3
LEE [71]	2008	SES(n = 200), PES (n =200)	Men (61.0%) Men(55.0%)	Age (years) 61.1± 8.9 , Age (years), 60.7 ±8.8
EUROSTAR[72]	2011	PES (n=152) BMS (n=151)	Male (74.3%), Male (68.9%)	Age (years) 64.9±9.2, Age (years) 66.2±9.4
EXAMINATION [73]	2012	EES (n=751 BMS (n=747)	Male (82%) Male (84%),	Age (years), 60±8 Age (years), 61±6
ISAR LEFT MAIN[74]	2009	PES (n = 302) SES (n = 305)	Male (23%), Male (38%)	Age, (years) 68.8± 10.1 Age, (years) 69.3 ± 9.34,
JUWANA [75]	2009	SES(n = 196) PES(n=201)	Men (69%), Men(74%)	Age (years) 61± 11,
KIM [76]	2008	SES (n = 85), PES (n = 84)	Male (71.8%), Male (76.2%)	Age (years) 62.9 ± 8.0 , Age (years) 61.5 ± 8.9

LEADERS[77]	2008	BES (n=857) SES(n=850)	Men (75%), Men (74%)	Age (years) 64.6 ±10.8, Age (years) 64.5 ±10.7
LONG DES II[78]	2006	SES (n=250) PES(n=250)	Male (67.2%) Male (61.2%)	Age (years)61.4 Age (years) 60.7
LONG DES III[79]	2 0 1 1	EES (n = 224) SES(n =226)	Male (73.7%), Male(65.9%)	Age, (years) 62.9 Age, (years) 63.0
LONG DES IV[80]	2012	RESOLUTE-ZES (n= 250) SES (n=250)	Male , (73.6%) Male, (72.4%)	Age (years)62.8±9.7, Age,(years)62.7±9.8,
LIPSIA[81]	2 0 1 1	SES(n= 120) PES(n= 116)	Male (69%), Male (68%)	Age(years) ,67.0±9.5 Age (years), 67.3±9.1,
MISSION [82]	2008	SES (n = 158) BMS (n = 152)	Male (69%), Male (68%)	Age (years) 59.2 Age (years) 59.1
MULTISTRATEGY[83]	2008	Abciximab Plus BMS(n = 186) Abciximab Plus (n = 186) Tirofiban Plus BMS (n = 186) Tirofiban Plus SES(n = 186)	Male (73.1%), Male (72.6%), Male (79.5%), Male (78.5%)	Age, (years) 63.9 ±11.7, Age, (years) 62.7± 11.2 Age, (years) ,65.4 ±12.1 Age,(years),63.4±12,
Natsuaki [84]	2013	BES (n=1617) EES (n=1618)	Male (77%), Male (77%)	Age (years) 69.1±9.8, Age (years) 69.3±9.8,
PACHE MEHILI [85]	2005	PES (n= 250) BMS(n = 250)	Men (78%) Men (78%)	Age (years) , 67.4±16.4 Age, (years) 66.7 ± 14.8
PAINT[86]	2009	PES (n =111) BMS(n = 57) SES(n = 106)	Men (61.3 %) Men (67.0%) Men (66.7%),	Age, (years) 60.1 ± 10.2 Age, (years)59.7 ±10.6, Age, (years)58.5 ± 9.6
PROSIT[87]	2008	SES (n= 154) PES (n = 154)	Male (76.0%) Male(76.6%)	Age (years) 60 .6 ±11 Age(years),60 .6 ±12
NOBORI[88]	2011	BES(n =194) SES(n =132)	Male (71.6%), Male (72.0%)	Age (years) 67.1 ± 10.3 Age (years)67.7 ± 9.3,

PAN[89]	2012	SES(n = 145) EES(n = 148)	Male (79%) Male (82%),	Age (years) 63 ± 10 Age (years) 63 ± 11
RAVEL[90]	2002	SES (n=120) BMS (n=118)	Male (70%), Male (81%)	Age (years) 61.8±10.7, Age (years) 59.7±10.1,
REALITY[91]	2006	SES(n = 684) PES(n = 669)	Men (72.0%), Men (74.1%)	Age (years) 62.6 ±10.5, Age (years) 62.6 ± 10.0,
REMEDEE[92]	2013	SES(n = 124) PES(n=59)	Men (71.8%), Men(71.2%)	Age (years) 64.20 ±9.48 Age (years) 64.05 ± 10.49
RESET[93]	2013	SES (n=1600) EES (n=1597)	Male (12.17%), Men(76%)	Age(years) 68.9±9.7, Age (years) 69.3±9.6,
RESOLUTE[94]	2013	RESOLUTE ZES(n=198) PES(n = 202)	Male (77.8%), Male (80.7%)	Age, (years) 59.7±9.9, Age, (years)59.6±10.6,
SEPARHAM [95]	2011	BES (n=100) EES (n=100)	Male (66%) Male (64%)	Age, (yrs)60.60±9.1, Age, (yrs) 62.38±10.2
SESAMI [96]	2007	SES (n = 160) BMS (n = 160)	Male (80%), Male (80%),	Age (years) 63±20, Age (years) 62 ±16
SEZE[97]	2012	ZES (n=60) SES (n=61)	Male (81.6%) Male (80.3%)	Age (years) 59.8±13.3 Age (years) 62.0±11.5
SERRYUS[98]	2010	ZES (N = 1152) EES (N = 1140)	Male (76.7%), Male (77.2%),	Age (years) 64.2±10.8 Age(years) 64.4±10.9
SORT OUT IV[99]	2012	SESn=1384 EES n=1390	Men (75.5%), Men (72.4%).	Age (years) 64.1± 10.8, Age(years) 63.5 ±13.2,
SORT OUT V [100]	2013	BES(n=1229) SES(n=1239)	Men (74·6%), Men (75·1%)	Age (years) 65·0 ±10·6, Age (years) 65·2 ±10·3,

SPIRIT III STONE [101]	2008	EES (n=669) PES (n= 332)	Men (70.1%), Men (10.2%)	Age, (years) 63.2± 10.5, Age (years) 62.8 ±10.2,
SPIRIT IV [102]	2013	EES (n = 2458) PES (n = 1229)	Male (67.7%), Male (67.8%)	Age (years) 63.3±10.5 Age (years) 63.3±10.2
SPIRIT V [103]		EES(n = 218) PES(n = 106)	Male (70 %) Male (67%)	Age (years) 65 ± 10 Age (years) 66 ± 9,
STEALTH[104]	2005	BES (n=80) BMS (n=40)	Male (48%), Male (33%)	Age (years) , 62.2 ± 10.1 Age (years) , 61.1 ± 9.4,
ZEST AMI [105]	2009	ZES n=(108) SES (n = 110) PES (n =110)	Male (77.8%) Male (86.4%) Male (82.7%)	Age, (years) 61.9 ± 11.0, Age (years), 57.8 ± 11.3 Age (years) , 59.3 ± 11.2
TAXI [106]	2005	PES (n = 100) SES(n = 102)	Male(83%) Male (79/%),	Age (years) 63 ± 10 Age (years) 65± 10
TAXUS VI[107]	2005	PES (n = 577) , BMS (n = 579)	Male (70.2%), Male (68.7%)	Age (years) 62.9 ± 11.2, Age, (years) 62.8 ±10.8,
TAXUS[108]	2005	PES (n=219) BMS(n=227),	Male, (76.3%) Male, (76.2%)	Age (years)61.8±9.7, Age (years) 63.4±9.9,
TYPHHON [109]	2006	SES(N = 355) BMS(N = 357)	Male (78.6%), Male (78.2%),	Age (years) 58.0, Age (years) 60.5,
TWENTE[110]	2012	RESOLUTE ZES (n =697), EES (n=694)	Men (72.5%), Men (72.6%)	Age (years) 64.2 ± 10.8 , Age (years) 63.9± 10.9, Age (years) 64.5 ± 10.7
XAMI[111]	2012,	EES (n=404) SES (n = 221)	Male (73.0%) Male (75.1%)	Age (years) 61.2 ± 11.3, Age (years) 62.0± 11.4

ZEST[112]	2010	ZES (n=883) SES (n =878) PES (n=884)	Male (66.4%), Male (67.3%), Male (65.8%)	Age, (years) 61.7± 9.3, Age, (years) 61.9 ±9.6 Age, (years) 62.0 ± 9.6,
ZOMAXX[113]	2011	ZES(n=557) PES(n=542),	Male (69%), Male (69%)	Age (years) 63±10 Age (years) 63±11

BASKET PROVE KAISER [114]	*2013*	EES (n=774) SES (n=775) BMS (n=774)	Male(76%)Male(74%) Male(77%)	Age(years) 66±11 Age (years)66±11 Age (years) 67±11
Byrne[115]	2010	SES (n = 335), ZES (n = 339).	Male (77.3%) Male (75.5%)	Age (years) 66.6±11.1 Age (years)67.2 ±10.9
COMPARE[116]	2011	EES (n = 897) PES (n = 903)	Male(69%) Male (72%)	Age (years)62.9 ± 15.7,Age (years) 63.6±17.2
DES DIABETES[117]	2011	SRL(n=200) PES(n =200)	Male (61%) Male (55%)	Age (years) 61.1±8.9 Age (years)60.7± 8.8,
ENDEAVOR II FIVE YEARS[118]	2010	ZES(n= 598), BMS(n =599)	Male(77.2%) Male (75.4%)	Age, (years) 61.6±10.5 Age, (years) 61.9±10.5
ENDEAVOR III 5 YEARS [119]	2011	ZES (n = 323), SES (n=113)	Male(65.3%) Male(81.4%)	Age (years), 61.42±10.58 Age (years), 61.73±11.59 ,
ENDEAVOR IV[120]	2013	ZES(n= 773) PES(n= 775)	Male(66.9%) Male(68.5%)	Age, (years)63.5±11.1 Age, (years)63.6±11.0
GISSOC [121]	*2010*	BMS(n = 78) SES(n = 74)	Male (87.1%), Male (78.3%)	Age (years) 63.9±9.8, Age

				(years)63.9± 9.6,
HONG[122]	2010	SES (n =85) PES (n =84)	Male (71.8%) Male (76.2%)	Age (years) 65.9± 8.0, ,Age (years) 64.5± 8.9,
HORIZON AMI[123]	2011	Heparin plus a GPI(n=1802), Bivalirudin monotherapy(n =1800) PES(n=2257), BMS(n=749)	Male (76%) Male (77%), Male (76%)	*Age (years) 60.7± 17.2* *Age (years) 59.8*±17.6 *Age (years) 59.9*±17, *Age (years) 59.3*±17.4
ISAR LEFT MAIN [124]	2009	PES (n = 302) SES (n = 305)	Male(75%) Male(80%)	Age, (years) 68.8 ± 10.1 Age (years) 69.3 ±9.34
Klaus [125]	2011	BES (n = 857), SES (n = 850),	Male (75%) Male (74.6%)	Age, (years) 64.6±10.8 Age, (years) 64.5±10.7
KOMER[126]	2011	ZES (n=205) SES (n=204) PES (n=202)	Male(76%) Male(81%) Male(79%)	Age, (years) 60±13 Age (years), 59±12, Age(years) ,60±13,
Leaders [127]	2011	BES(n= 857) , SES(n= 850)	Men (75%), Men (74%)	Age (years) 64.6 ±10.8, Age (years) 64.5 ±10.7
LATE [128]	2011	SES (n=503), PES(n= 509)	Male(76%), Male(78%)	Age (years) 62±11 Age (years) 62±12
MISSION [129]	2012	SES (n=158) BMS (n=152	Men (74.7%) Male(80.9%)	Age (yrs) 59.2±11.2 Age (yrs) 59.1±11.6
NAPLES DIABETES [130]	2011	SES (n=76) PES (n=75), EES (n=75)	Male (57%), Male (59%) , Male (56%)	Age, (years) 64±8, Age, (years) 64±10 Age, (years) 65±8,
MULTISTRATEGY [131]	2013	SRL(n= 370) BMS(n=372)	Male (73.1%) Male (72.6%)	Age (years)63.9 ±11.7 Age (years)

				62.7 ± 11.2 Age (years) 65.4 ±12.1 Age (years) 63.4 ±12
PAINT [132]	2012	PES (n=111) SES (n=106) BMS(n=57)	Male(61.3 %) Male(67.0%) Male(66.7%)	Age, (years) 60.1±10.2 Age (years) 59.7±10.6 Age (years) 58.5±9.6
PASEO [133]	2009	BMS (n = 90) PES (n =90)	Male(71.1%) Male(68.9%)	Age, (years) 62± 17, Age (years) 63± 15
PASSION [134]	2011	PES(n= 310) BMS (n = 309)	Male(73.9%) Male(78%)	Age, (years) 61±12, Age, (years) 61±13
PRISON[135]	2012	BMS(n=100) SES (n=100)	Male (76%) Male(83%)	Age (years) 59.3±10.2 Age (years) 59.6±10.6
PROTECT [136]	2012	EES (n=4357) SES (n=4352)	Male(77%) Male (76%)	Age (years) 62·3 ±10·6, Age (years) 62·1± 10·7
PROSIT [137]	2011	SES (n = 154) PES (n = 154)	Male(76%) Male(76.6%)	Age (years), 60 .6 ±11, Age (years), 60. 6 ±12
PURICEL [138]	2013	ERL(n= 200) BES(n= 200)	Male(75.5%) Male(73%)	Age (years) 65.9±11.2 Age (years) 64.9±10.
RAVEL [139]	2007	SES(n= 120) BMS (n=118)	Male(70%/) Male(81%)	Age (years) 61.8±10.7 Age (years) 59.7±10.1
RESOLUTE[140]	2011	RESOLUTE - ZES(N=1140) EES(N=1152)	Male(76.7%) Male(77.2%)	Age (years) 64·4 ± 10·9, Age (years) 64·2 ± 10·8

SCOPRIUS[141]	2012	SES (n = 95) BMS (n = 95)	Male(66%) Male(62%)	Age (years) 66 ± 9, Age (years) 66 ± 10
SEASIDE [142]	2011	SES (n= 75) ERL (n= 75)	Male(75%) Male(85%)	Age, (years) 64±10
SESAMI[143]	2011	SES(n=155) BMS (n=155)	Male(82%) Male(81%)	Age, (years) 63±15, Age (years) 63± 19
SIRTAX [144]	2008	SES(n= 503) PES (n = 509)	Males (69.4%) Male(72.0%) Male (79.8%)	Age (years) 62 ± 10
SORT OUT III 18 MONTHS [145]	2010	ZES (n = 1,162) SES (n =1,170)	Male(73%) Male(74%)	Age(years), 64.3± 10.7 Age (years), 64.3± 10.8
SORT OUT III[146]	2012	ZES (n = 1,162) SES (n = 1,170)	Male(73%) Male(74%)	Age, (years) 64.3± 10.7, Age (years) 64.3±10.8
SORT OUT IV [147]	2012	EES (n=1390), SES (n=1384),	Male(75.9%) Male(75.2%)	Age years , 64.2 ±10.9, Age years, 64.0±10.8
SPIRIT II 3 YEARS [148]	2009	EES (n = 223) PES (n = 77)	Male(71%) Male(79%)	Age (years) 62±10, Age (years) 62±9
TAXI LATE [149]	2007	SES(n= 100) PES (n= 102)	Male(77%), Male(83%)	Age (years), 65. 6±10, Age (years) ,63. 6± 10
TAXUS [150]	2011	BMS (n=1397) PES (n=1400)	Age (81,7%) Age (71.5%)	Age (years), 62.2±10.7 Age (years), 62.8±11.0
TAXUS IV[151]	2009	BMS (n=643) PES (n = 651	Male (72.2%) Male(71.7%)	Age (years) 62.1±11.0 Age (years)

TAXUS VI[152]	2009	BMS (n=233) PES(n =217)	Male (70.2%), Male (68.7%)	62.8±11.2 Age (years) 62.9 ± 11.2, Age, (years) 62.8 ±10.8,
TWENTE[153]	2013	Resolute- ZES (n= 697) EES(n= 694)	Men (72.5%) Men (72.6%)	Age (years) 63.9 ± 10.9, Age (years) 64.5 ± 10.7
Typhoon[154]	2011	SES (n=355) BMS (n=357)	Male (77.7%) Male(78.6%)	Age, (years) 59.3±13.2 Age, (years) 59.2±11.7,
ZOMAXX[155]	2013	ZES (n=199) PES (n=197)	Male (75%) Male(77%)	Age (years) 63 ± 10 Age (years) 63 ± 11

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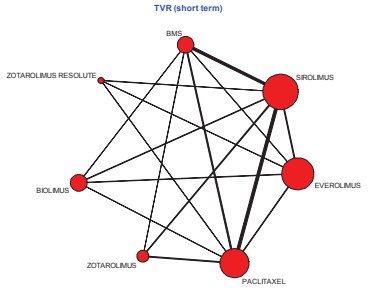
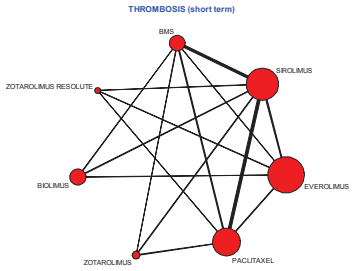
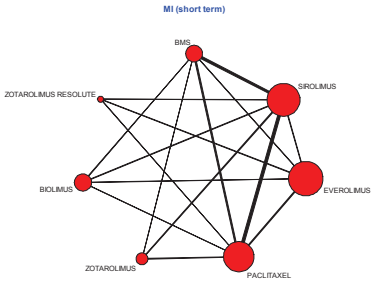
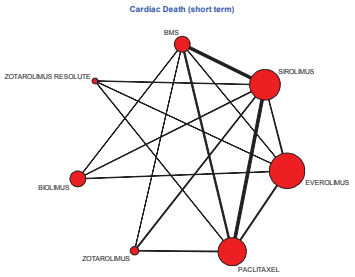
Figure 1

SHORT TERM CHECK

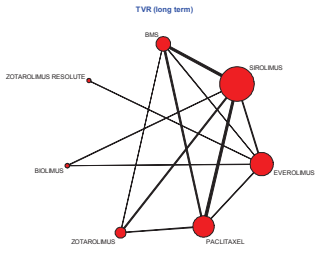


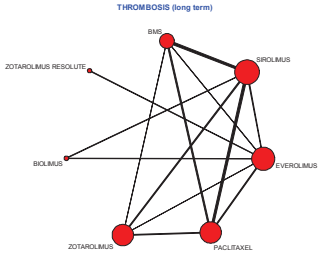


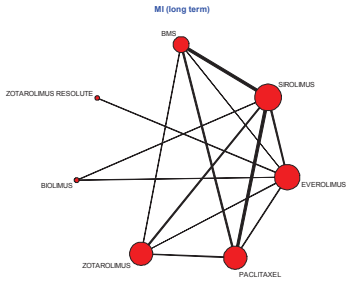




LONG TERM CHECK







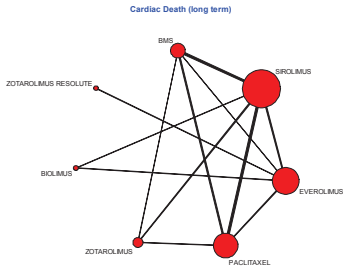
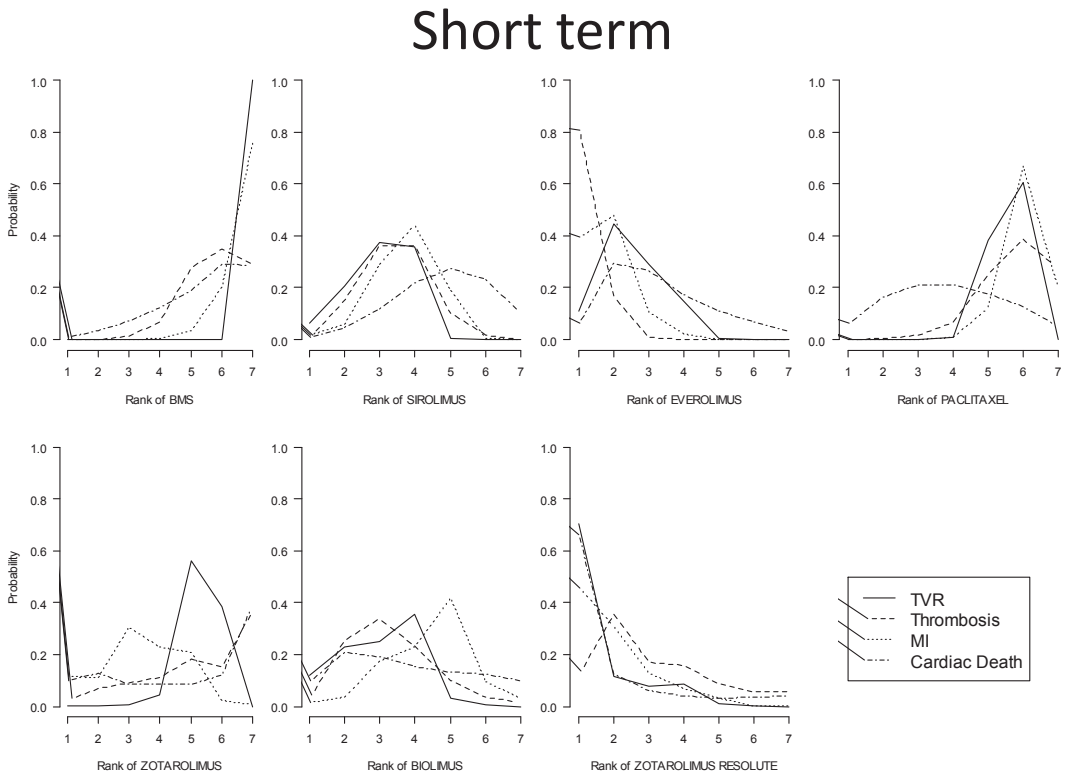


Figure 2


Short term
Probability
Rank of BMS
Rank of SIROLIMUS
Rank of EVEROLIMUS
Rank of PACLITAXEL
Rank of ZOTAROLIMUS
Rank of BIOLIMUS
Rank of ZOTAROLIMUS RESOLUTE
TVR
Thrombosis
MI
Cardiac Death

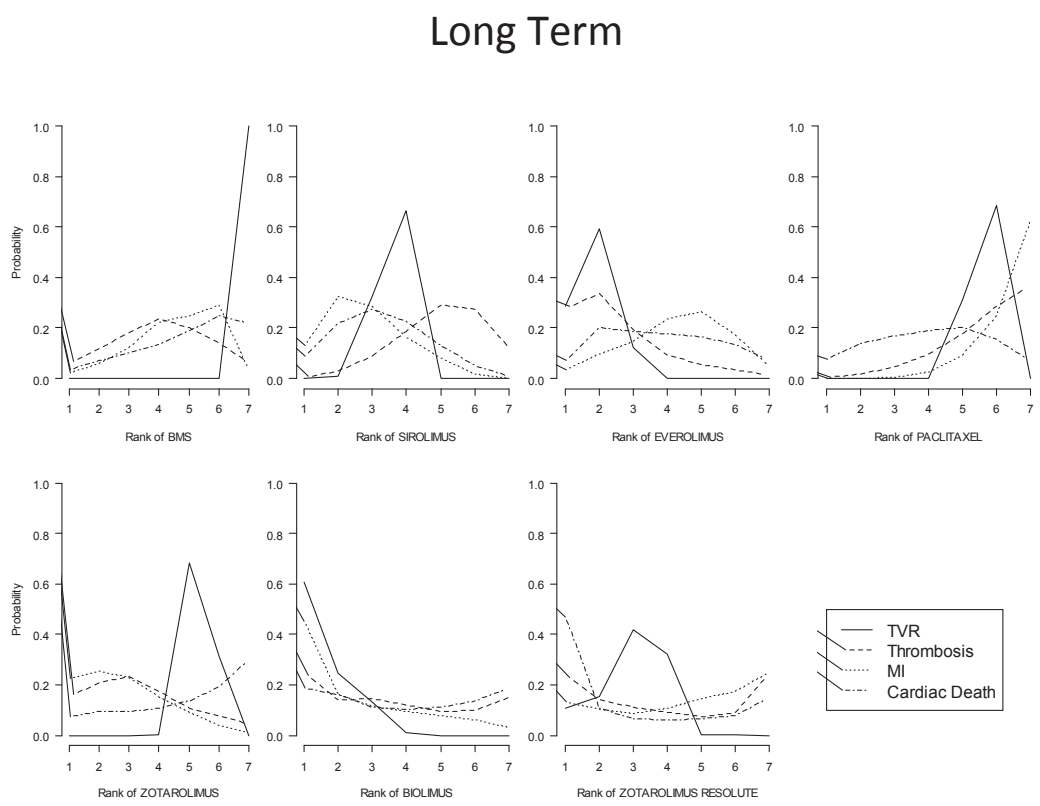
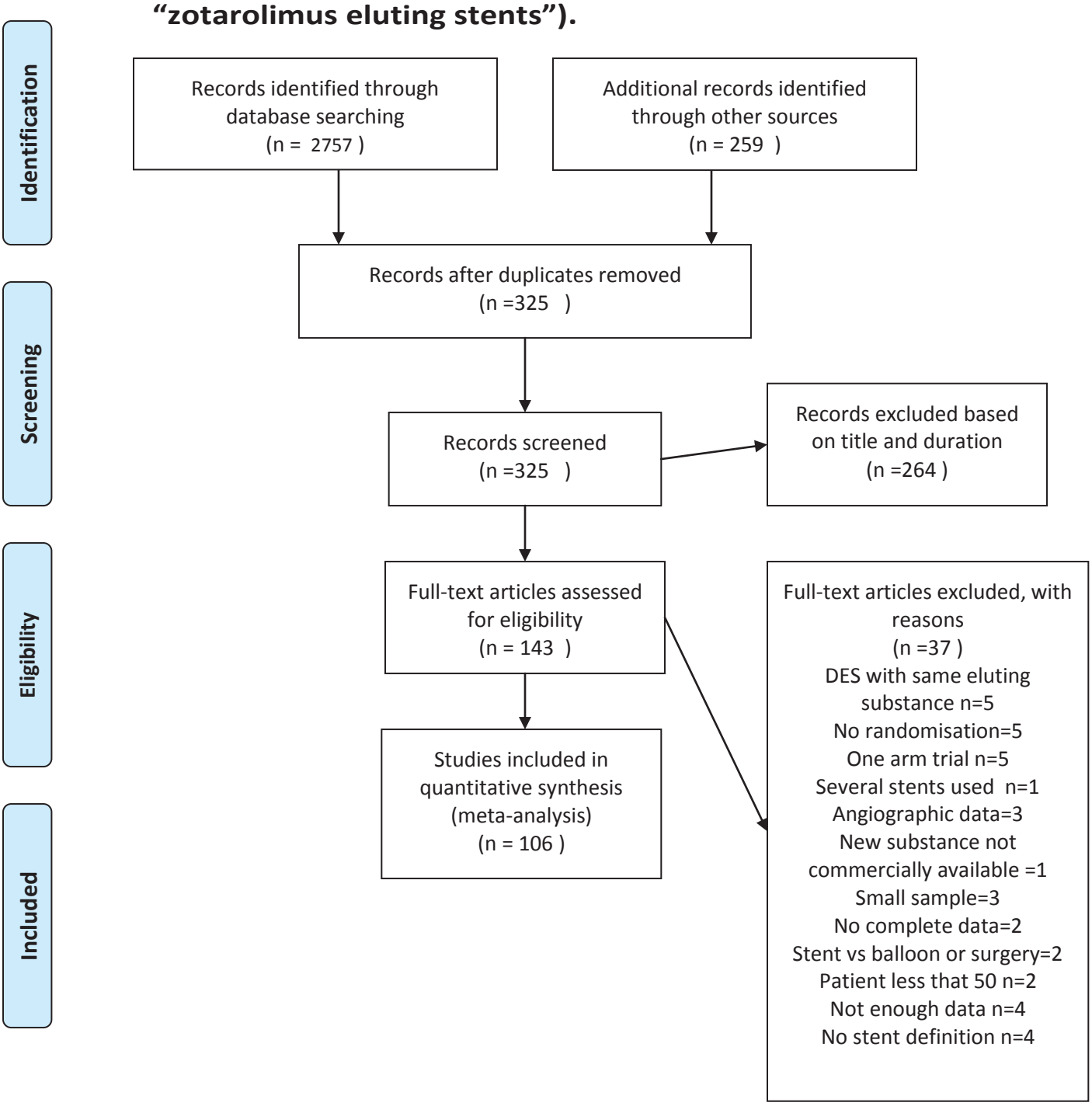

Long Term
Probability
Rank of BMS
Rank of SIROLIMUS
Rank of EVEROLIMUS
Rank of PACLITAXEL
Rank of ZOTAROLIMUS
Rank of BIOLIMUS
Rank of ZOTAROLIMUS RESOLUTE
TVR
Thrombosis
MI
Cardiac Death

Table 1

PRISMA 2009 Flow(Mesh terms "sirolimus eluting stents", "paclitaxel eluting stents", "drug eluting stent" , "Endeavor zotarolimus stent", " biodegradable stent" "everolimus eluting stents", "zotarolimus resolute eluting stent", "biolimus eluting stent" and "zotarolimus eluting stents").



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 2

TABLE 2. LONG TERM PROBABILITY

AGENT	PROBABILITY BEST % REDUCING CARDIAC DEATH FIXED EFFECT	PROBABILITY BEST % REDUCING MI RANDOM EFFECT	PROBABILITY BEST % REDUCING TVR FIXED EFFECT	PROBABILITY BEST % REDUCING THROMBOSIS RANDOM EFFECT
BMS	3.6	2	0	6
SIROLIMUS	8.7	12	0	0.5
EVEROLIMUS	6.9	3	28.5	27.8
PACLITAXEL	7.2	0	0	0.5
ZOTAROLIMUS	7.4	22.4	0	15
BIOLIMUS	18.7	45	60.8	25
ZOTAROLIMUS RESOLUTE	47.37	13	10.5	24.5

Table 3

Table 3. Odds ratio Long Term

	Comparator	CARDIAC DEATH ODDs RATIO FE	95% CI	MI ODDS RATIO RE	95% CI	TVR ODDs RATIO FE	97.5% CI	THROMBOSIS ODDS RATIO RE	97.5% CI
BMS									
	SIROLIMUS	0.92	0.73-1.13	0.87	0.67-1.12	0.401*	0.35-0.45*	1.09	0.79-1.46
	EVEROLIMUS	0.94	0.71-1.22	0.99	0.69-1.46	0.33*	0.28-0.39*	0.86	0.52-1.34
	PACLITAXEL	0.95	0.78-1.15	1.20	0.94-1.53	0.61*	0.55-0.68*	1.17	0.84-1.58
	ZOTAROLIMUS	1.01	0.73-1.37	0.87	0.61-1.22	0.59*	0.50-0.70*	0.94	0.60-1.44
	BIOLIMUS	0.95	0.65-1.35	0.82	0.47-1.30	0.32*	0.25-0.40*	0.98	0.50-1.76
	RESOLUTE	0.88	0.50-1.42	1.07	0.56-1.93	0.38*	0.28-0.50*	1.03	0.42-2.14
SIROLIMUS									
	EVEROLIMUS	1.02	0.83-1.25	1.15	0.81-1.62	0.84*	0.74-0.95*	0.79	0.50-1.18
	PACLITAXEL	1.04	0.85-1.26	1.39	1.08-1.76	1.54	1.36-1.74*	1.08	0.79-1.42
	ZOTAROLIMUS	1.10	0.84-1.42	1.00	0.73-1.35	1.48	1.26-1.73*	0.86	0.58-1.26
	BIOLIMUS	1.04	0.76-1.38	0.94	0.57-1.40	0.80*	0.66-0.97*	0.89	0.49-1.51
	RESOLUTE	0.95	0.57-1.50	1.23	0.66-2.18	0.94	0.71-1.23	0.95	0.40-1.92
EVEROLIMUS									
	PACLITAXEL	1.02	0.79-1.30	1.24	0.84-1.69	1.84	1.56-2.15*	1.41	0.88-2.13
	ZOTAROLIMUS	1.08	0.77-1.48	0.89	0.59-1.24	1.77	1.45-2.14*	1.13	0.70-1.77
	BIOLIMUS	1.02	0.70-1.42	0.84	0.44-1.35	0.96	0.76-1.20	1.18	0.56-2.22
	RESOLUTE	0.93	0.58-1.40	1.07	0.63-1.68	1.12	0.87-1.42	1.20	0.59-2.19

PACLITAXEL									
	ZOTAROLIMUS	1.06	0.77-1.43	0.72	0.52-0.99*	0.96	0.81-1.13	0.81	0.54-1.20
	BIOLIMUS	1.00	0.69-1.40	0.68	0.39-1.07	0.52*	0.41-0.65*	0.84	0.43-1.51
	RESOLUTE	0.92	0.53-1.47	0.89	0.47-1.58	0.61*	0.45-0.81*	0.89	0.37-1.82
ZOTAROLIMUS									
	BIOLIMUS	0.95	0.62-1.39	0.96	0.52-1.54	0.54*	0.42-0.69*	1.072	0.51-1.96
	RESOLUTE	0.88	0.48-1.46	1.24	0.65-2.22	0.64*	0.46-0.86*	1.124	0.45-2.29
BIOLIMUS									
	RESOLUTE	0.94	0.51-1.58	1.37	0.64-2.80	1.18	0.83-1.63	1.147	0.39-2.6
Median estimate of heterogeneity (95% CrI)		NA		0.23	0.03-0.48	NA		0.27	0.03-0.53

* evidence of a significant effect

Table 4

TABLE 4 SHORT TERM PROBABILITY

AGENT	PROBABILITY BEST % REDUCING CARDIAC DEATH FIXED EFFECTS	PROBABILITY BEST % REDUCING FIXED EFFECTS MI	PROBABILITY BEST % REDUCING TVR RANDOM EFFECTS	PROBABILITY BEST % REDUCING THROMBOSIS FIXED EFFECTS
				0
BMS	0.9	0	0	0
SIROLIMUS	0.98	1.5	6.1	0.5
EVEROLIMUS	5.9	39.2	11.1	82
PACLITAXEL	5.9	0	0	0
ZOTAROLIMUS	10	11.6	0	2.3
BIOLIMUS	9.4	1.3	12	2.5
ZOTAROLIMUS RESOLUTE	66.7	46	70	12

Table 5

Table 5. Odds Ratio Short Term

	Comparator	CARDIAC DEATH ODDs RATIO FIXED EFFECTS	97.5% CI	MI ODDS RATIO FIXED EFFECTS	97.5% CI	Comparator	TVR ODDs RATIO RANDOM EFFECTS	97.5% CI	THROMBOSIS ODDS RATIO FIXED EFFECTS	97.5% CI
BMS										
	SIROLIMUS	0.95	0.72-1.23	0.74*	0.60-0.90*	SIROLIMUS	0.28*	0.22-0.36*	0.79	0.57-1.08
	EVEROLIMUS	0.85	0.61-1.16	0.62*	0.48-0.79*	EVEROLIMUS	0.27*	0.18-0.36*	0.53	0.34-0.77*
	PACLITAXEL	0.9	0.66-1.20	0.92	0.75-1.12	PACLITAXEL	0.45*	0.34-0.58*	1.00	0.67-1.44
	ZOTAROLIMUS	1.03	0.55-1.75	0.73*	0.54-0.96*	ZOTAROLIMUS	0.44*	0.29-0.61*	0.99	0.48-1.82
	BIOLIMUS	0.89	0.60-1.27	0.79	0.58-1.04	BIOLIMUS	0.29*	0.18- 0.42*	0.76	0.47-1.19
	RESOLUTE	0.69	0.35-1.22	0.63*	0.45-0.85*	RESOLUTE	0.22*	0.11-0.38*	0.71	0.32-1.36
SIROLIMUS										
	EVEROLIMUS	0.90	0.68-1.17	0.84	0.68-1.03	EVEROLIMUS	0.94	0.69-1.24	0.67	0.46-0.93*
	PACLITAXEL	0.94	0.72-1.22	1.24	1.05-1.47	PACLITAXEL	1.59*	1.27-1.97*	1.29	0.87-1.81
	ZOTAROLIMUS	1.08	0.59-1.81	0.98	0.75-1.25	ZOTAROLIMUS	1.53*	1.10-2.09*	1.27	0.61-2.27
	BIOLIMUS	0.94	0.66-1.29	1.06	0.83-1.35	BIOLIMUS	1.01	0.68 -1.42	0.97	0.63-1.43
	RESOLUTE	0.73	0.38-1.26	0.85	0.62-1.12	RESOLUTE	0.78	0.41 -1.32	0.90	0.42-1.65
EVEROLIMUS										
	PACLITAXEL	1.06	0.76-1.44	1.48*	1.20-1.8*	PACLITAXEL	1.71*	1.27-2.28*	1.94	1.28-2.81*
	ZOTAROLIMUS	1.22	0.64-2.11	1.17	0.85-1.55	ZOTAROLIMUS	1.65*	1.08-2.45*	1.92	0.90-3.56
	BIOLIMUS	1.05	0.73-1.46	1.26	0.99-1.60	BIOLIMUS	1.08	0.72 -1.56	1.47	0.93-2.25
	RESOLUTE	0.81	0.45-1.33	1	0.80-1.23	RESOLUTE	0.83	0.46-1.35	1.34	0.69-2.35
PACLITAXEL										
	ZOTAROLIMUS	1.15	0.64-1.91	0.79*	0.61-1.00*	ZOTAROLIMUS	0.96	0.68-1.33	0.99	0.51-1.75
	BIOLIMUS	1.00	0.66-1.46	0.85	0.65-1.11	BIOLIMUS	0.63*	0.42-0.92*	0.77	0.46-1.25
	RESOLUTE	0.78	0.40-1.37	0.68	0.50-0.90*	RESOLUTE	0.49*	0.26-0.82*	0.71	0.33-1.35
ZOTAROLIMUS										
	BIOLIMUS	0.93	0.47-1.66	1.10	0.77-1.52	BIOLIMUS	0.67	0.40-1.04	0.85	0.38-1.7
	RESOLUTE	0.72	0.30-1.48	0.87	0.60-1.24	RESOLUTE	0.52*	0.25-0.93*	0.79	0.28-1.74
BIOLIMUS										
	RESOLUTE	0.79	0.39-1.41	0.80	0.57-1.09	RESOLUTE	0.79	0.39-1.42	0.95	0.42-1.83
Median estimate of heterogeneity		NA		NA			0.34	0.20-0.50	NA	

(95% CrI)

* Evidence of a significant effect

Table 6. Included Studies

Study	Year	Comparative Arms	Sex	Age
BASKET [50]	2005	SES (n=264), PES (n=281), BMS (n=281)	Male (79%) Male (79%)	Age (years) 64±11 Age (years) 64±12
CATOS[51]	2012	ZES (n=80) SES (n=80),	Male (65%) Male (76%)	Age (years) 62.7±12.3 Age (years) 63.0±11.7
C-SIRIUS[52]	2004	SES(n = 50), BMS(n =50)	Male (70 %) Male (68%)	Age (years) 60.3 ±10.6, Age (years) 60.7± 9.1,
CHEVALIER [53]	2007	BES (n=85),PES (n=35)	Male (69 %) Male (66%)	Age (years) 65±11, Age (years) 63±11
COMFORTABLE AMI[54]	2012	BES (n = 575) BMS(n = 582),	Male (80.5%), Male (78.2%)	Age ,(years) 60.7± 11.6, Age, (years), 60.4 ± 11.9
COMPARE [55]	2010	EES(n=897), PES (n=903)	Male (69%), Male (72%)	Age (years)62.9 ± 15.7,Age (years) 63.6±17.2
COMPARE II[56]	2013	BES(n=1795) EES(n=912)	Male (74. 4%), Male(74.3%)	Age (years) 63± 11.1, Age (years) 62.7± 11.0
DEBATER[57]	2 0 1 2	SES (n =424) BMS (n = 446 Abciximab(n = 439) , No Abciximab (n = 434)	Male (78%), Male (75%), Male (76%) Male (78%)	Age(years) 60±11 Age (years) 61±11 Age (years) 60±10 , Age, (years)60±12
DESSERT[58]	2008	SES(n = 75) BMS (n = 75)	Male(63%), Malen(49%)	Age (years) 71 ±9 Age (years) 69±9,
DIABEDES[59]	2007	SES(n = 76) PES(n =77)	Male (84%) Male (74%),	Age (years) 66 ±8, Age (years) 65 ±10
DIABETES[60]	2005	SES (n = 80) BMS (n = 80)	Male (70%) Male (81%)	Age (years) 65.9±9 6 Age (years) 7.2±10
DIAS DE LA LIERA[61]	2007	BMS (n = 54), SES (n = 60)	Male (78.3%) , Male (80.0)	Age, (years) 65 ±13 64
DIBRA[62]	2005	BMS(N=125), SES(N=125),	Male (64%), Male (68%)	Age (years) 68.3±9.6 Age (years) 67.7±10.2
E-SIRIUS[63]	2003	SES (n=175), BMS (n=177),	Men (70%), Men 126 (71%),	Age (years) 62·0 ±11·4, age (years)62·6±10·3,
ENDEAVOR II[64]	2006	EES(n=598),	Male (77%),	Age(years)61.6±10.5,

ENDEAVOR III[65]	2006	BMS (n=599) ZES(n=323), SES (n=113)	Male (75%) Male (65.3 %) Male (81.4 %)	Age (years) ,61.9±10.5 Age (years) 61.42 ±10.58, Age (years) 61.73 ±11.59
ENDEAVOR IV [66]	2010	ZES (n =773) PES (n =775),	Men (66.9%) Men (68.5%)	Age, (years) 63.5± 11.1 Age(years)63.6 ± 11.0
ESSENCE DIABETES[67]	2013	EES(n=149) SES(n=151)	Men (52.3%) ,Men (65.6%)	Age (years) 63.2±8.3, Age (years)63.5±8.1
EXCELLENT[68]	2011	EES (n = 1,079), SES (n = 364)	Male (65.2%) Male (62.6%)	Age (years) 62.5 ±10.1 Age (years) 63.4 ±9.9
Erglis[69]	2007	BMS (n =50)), PES (n = 53)	Male (82%) Male (85%)	Age (years) 62.56 ±11.45, Age(years) 61.08± 10.28,
HORIZON AMI STONE [70]	2009	PES(N = 2257) BMS (N = 749)	Male . (77.0%), Male (76.0%)	Age (years) 59.9 Age (years) 59.3
LEE [71]	2008	SES(n = 200), PES (n =200)	Men (61.0%) Men(55.0%)	Age (years) 61.1± 8.9 , Age (years), 60.7 ±8.8
EUROSTAR[72]	2011	PES (n=152) BMS (n=151)	Male (74.3%), Male (68.9%)	Age (years) 64.9±9.2, Age (years) 66.2±9.4
EXAMINATION [73]	2012	EES (n=751 BMS (n=747)	Male (82%) Male (84%),	Age (years), 60±8 Age (years), 61±6
ISAR LEFT MAIN[74]	2009	PES (n = 302) SES (n = 305)	Male (23%), Male (38%)	Age, (years) 68.8± 10.1 Age, (years) 69.3 ± 9.34,
JUWANA [75]	2009	SES(n = 196) PES(n=201)	Men (69%), Men(74%)	Age (years) 61± 11,
KIM [76]	2008	SES (n = 85), PES (n = 84)	Male (71.8%), Male (76.2%)	Age (years) 62.9 ± 8.0 , Age (years) 61.5 ± 8.9
LEADERS[77]	2008	BES (n=857) SES(n=850)	Men (75%),	Age (years) 64.6 ±10.8, Age (years) 64.5 ±10.7

			Men (74%)	
LONG DES II[78]	2006	SES (n=250) PES(n=250)	Male (67.2%) Male (61.2%)	Age (years)61.4 Age (years) 60.7
LONG DES III[79]	2 0 1 1	EES (n = 224) SES(n =226)	Male (73.7%), Male(65.9%)	Age, (years) 62.9 Age, (years) 63.0
LONG DES IV[80]	2012	RESOLUTE-ZES (n= 250) SES (n=250)	Male , (73.6%) Male, (72.4%)	Age (years)62.8±9.7, Age,(years)62.7±9.8,
LIPSIA[81]	2 0 1 1	SES(n= 120) PES(n= 116)	Male (69%), Male (68%)	Age(years) ,67.0±9.5 Age (years), 67.3±9.1,
MISSION [82]	2008	SES (n = 158) BMS (n = 152)	Male (69%), Male (68%)	Age (years) 59.2 Age (years) 59.1
MULTISTRATEGY[83]	2008	Abciximab Plus BMS(n = 186) Abciximab Plus (n = 186) Tirofiban Plus BMS (n = 186) Tirofiban Plus SES(n = 186)	Male (73.1%), Male (72.6%), Male (79.5%), Male (78.5%)	Age, (years) 63.9 ±11.7, Age, (years) 62.7± 11.2 Age, (years) ,65.4 ±12.1 Age,(years),63.4±12,
Natsuaki [84]	2013	BES (n=1617) EES (n=1618)	Male (77%), Male (77%)	Age (years) 69.1±9.8, Age (years) 69.3±9.8,
PACHE MEHILI [85]	2005	PES (n= 250) BMS(n = 250)	Men (78%) Men (78%)	Age (years) , 67.4±16.4 Age, (years) 66.7 ± 14.8
PAINT[86]	2009	PES (n =111) BMS(n = 57) SES(n = 106)	Men (61.3 %) Men (67.0%) Men (66.7%),	Age, (years) 60.1 ± 10.2 Age, (years)59.7 ±10.6, Age, (years)58.5 ± 9.6
PROSIT[87]	2008	SES (n= 154) PES (n = 154)	Male (76.0%) Male(76.6%)	Age (years) 60 .6 ±11 Age(years),60 .6 ±12
NOBORI[88]	2011	BES(n =194) SES(n =132)	Male (71.6%), Male (72.0%)	Age (years) 67.1 ± 10.3 Age (years)67.7 ± 9.3,

PAN[89]	2012	SES(n = 145) EES(n = 148)	Male (79%) Male (82%),	Age (years) 63 ± 10 Age (years) 63 ± 11
RAVEL[90]	2002	SES (n=120) BMS (n=118)	Male (70%), Male (81%)	Age (years) 61.8±10.7, Age (years) 59.7±10.1,
REALITY[91]	2006	SES(n = 684) PES(n = 669)	Men (72.0%), Men (74.1%)	Age (years) 62.6 ±10.5, Age (years) 62.6 ± 10.0,
REMEDEE[92]	2013	SES(n = 124) PES(n=59)	Men (71.8%), Men(71.2%)	Age (years) 64.20 ±9.48 Age (years) 64.05 ± 10.49
RESET[93]	2013	SES (n=1600) EES (n=1597)	Male (12.17%), Men(76%)	Age(years) 68.9±9.7, Age (years) 69.3±9.6,
RESOLUTE[94]	2013	RESOLUTE ZES(n=198) PES(n = 202)	Male (77.8%), Male (80.7%)	Age, (years) 59.7±9.9, Age, (years)59.6±10.6,
SEPARHAM [95]	2011	BES (n=100) EES (n=100)	Male (66%) Male (64%)	Age, (yrs)60.60±9.1, Age, (yrs) 62.38±10.2
SESAMI [96]	2007	SES (n = 160) BMS (n = 160)	Male (80%), Male (80%),	Age (years) 63±20, Age (years) 62 ±16
SEZE[97]	2012	ZES (n=60) SES (n=61)	Male (81.6%) Male (80.3%)	Age (years) 59.8±13.3 Age (years) 62.0±11.5
SERRYUS[98]	2010	ZES (N = 1152) EES (N = 1140)	Male (76.7%), Male (77.2%),	Age (years) 64.2±10.8 Age(years) 64.4±10.9
SORT OUT IV[99]	2012	SESn=1384 EES n=1390	Men (75.5%), Men (72.4%).	Age (years) 64.1± 10.8, Age(years) 63.5 ±13.2,
SORT OUT V [100]	2013	BES(n=1229) SES(n=1239)	Men (74·6%), Men (75·1%)	Age (years) 65·0 ±10·6, Age (years) 65·2 ±10·3,

SPIRIT III STONE [101]	2008	EES (n=669) PES (n= 332)	Men (70.1%), Men (10.2%)	Age, (years) 63.2± 10.5, Age (years) 62.8 ±10.2,
SPIRIT IV [102]	2013	EES (n = 2458) PES (n = 1229)	Male (67.7%), Male (67.8%)	Age (years) 63.3±10.5 Age (years) 63.3±10.2
SPIRIT V [103]		EES(n = 218) PES(n = 106)	Male (70 %) Male (67%)	Age (years) 65 ± 10 Age (years) 66 ± 9,
STEALTH[104]	2005	BES (n=80) BMS (n=40)	Male (48%), Male (33%)	Age (years) , 62.2 ± 10.1 Age (years) , 61.1 ± 9.4,
ZEST AMI [105]	2009	ZES n=(108) SES (n = 110) PES (n =110)	Male (77.8%) Male (86.4%) Male (82.7%)	Age, (years) 61.9 ± 11.0, Age (years), 57.8 ± 11.3 Age (years) , 59.3 ± 11.2
TAXI [106]	2005	PES (n = 100) SES(n = 102)	Male(83%) Male (79/%),	Age (years) 63 ± 10 Age (years) 65± 10
TAXUS VI[107]	2005	PES (n = 577) , BMS (n = 579)	Male (70.2%), Male (68.7%)	Age (years) 62.9 ± 11.2, Age, (years) 62.8 ±10.8,
TAXUS[108]	2005	PES (n=219) BMS(n=227),	Male, (76.3%) Male, (76.2%)	Age (years)61.8±9.7, Age (years) 63.4±9.9,
TYPHHON [109]	2006	SES(N = 355) BMS(N = 357)	Male (78.6%), Male (78.2%),	Age (years) 58.0, Age (years) 60.5,
TWENTE[110]	2012	RESOLUTE ZES (n =697), EES (n=694)	Men (72.5%), Men (72.6%)	Age (years) 64.2 ± 10.8 , Age (years) 63.9± 10.9, Age (years) 64.5 ± 10.7
XAMI[111]	2012,	EES (n=404) SES (n = 221)	Male (73.0%) Male (75.1%)	Age (years) 61.2 ± 11.3, Age (years) 62.0± 11.4

ZEST[112]	2010	ZES (n=883) SES (n =878) PES (n=884)	Male (66.4%), Male (67.3%), Male (65.8%)	Age, (years) 61.7± 9.3, Age, (years) 61.9 ±9.6 Age, (years) 62.0 ± 9.6,
ZOMAXX[113]	2011	ZES(n=557) PES(n=542),	Male (69%), Male (69%)	Age (years) 63±10 Age (years) 63±11

BASKET PROVE KAISER [114]	*2013*	EES (n=774) SES (n=775) BMS (n=774)	Male(76%)Male(74%) Male(77%)	Age(years) 66±11 Age (years)66±11 Age (years) 67±11
Byrne[115]	2010	SES (n = 335), ZES (n = 339).	Male (77.3%) Male (75.5%)	Age (years) 66.6±11.1 Age (years)67.2 ±10.9
COMPARE[116]	2011	EES (n = 897) PES (n = 903)	Male(69%) Male (72%)	Age (years)62.9 ± 15.7,Age (years) 63.6±17.2
DES DIABETES[117]	2011	SRL(n=200) PES(n =200)	Male (61%) Male (55%)	Age (years) 61.1±8.9 Age (years)60.7± 8.8,
ENDEAVOR II FIVE YEARS[118]	2010	ZES(n= 598), BMS(n =599)	Male(77.2%) Male (75.4%)	Age, (years) 61.6±10.5 Age, (years) 61.9±10.5
ENDEAVOR III 5 YEARS [119]	2011	ZES (n = 323), SES (n=113)	Male(65.3%) Male(81.4%)	Age (years), 61.42±10.58 Age (years), 61.73±11.59 ,
ENDEAVOR IV[120]	2013	ZES(n= 773) PES(n= 775)	Male(66.9%) Male(68.5%)	Age, (years)63.5±11.1 Age, (years)63.6±11.0
GISSOC [121]	*2010*	BMS(n = 78) SES(n = 74)	Male (87.1%), Male (78.3%)	Age (years) 63.9±9.8, Age

				(years)63.9± 9.6,
HONG[122]	2010	SES (n =85) PES (n =84)	Male (71.8%) Male (76.2%)	Age (years) 65.9± 8.0, ,Age (years) 64.5± 8.9,
HORIZON AMI[123]	2011	Heparin plus a GPI(n=1802), Bivalirudin monotherapy(n =1800) PES(n=2257), BMS(n=749)	Male (76%) Male (77%), Male (76%)	*Age (years) 60.7± 17.2* *Age (years) 59.8*±17.6 *Age (years) 59.9*±17, *Age (years) 59.3*±17.4
ISAR LEFT MAIN [124]	2009	PES (n = 302) SES (n = 305)	Male(75%) Male(80%)	Age, (years) 68.8 ± 10.1 Age (years) 69.3 ±9.34
Klaus [125]	2011	BES (n = 857), SES (n = 850),	Male (75%) Male (74.6%)	Age, (years) 64.6±10.8 Age, (years) 64.5±10.7
KOMER[126]	2011	ZES (n=205) SES (n=204) PES (n=202)	Male(76%) Male(81%) Male(79%)	Age, (years) 60±13 Age (years), 59±12, Age(years) ,60±13,
Leaders [127]	2011	BES(n= 857) , SES(n= 850)	Men (75%), Men (74%)	Age (years) 64.6 ±10.8, Age (years) 64.5 ±10.7
LATE [128]	2011	SES (n=503), PES(n= 509)	Male(76%), Male(78%)	Age (years) 62±11 Age (years) 62±12
MISSION [129]	2012	SES (n=158) BMS (n=152	Men (74.7%) Male(80.9%)	Age (yrs) 59.2±11.2 Age (yrs) 59.1±11.6
NAPLES DIABETES [130]	2011	SES (n=76) PES (n=75), EES (n=75)	Male (57%), Male (59%) , Male (56%)	Age, (years) 64±8, Age, (years) 64±10 Age, (years) 65±8,
MULTISTRATEGY [131]	2013	SRL(n= 370) BMS(n=372)	Male (73.1%) Male (72.6%)	Age (years)63.9 ±11.7 Age (years)

				62.7 ± 11.2 Age (years) 65.4 ±12.1 Age (years) 63.4 ±12
PAINT [132]	2012	PES (n=111) SES (n=106) BMS(n=57)	Male(61.3 %) Male(67.0%) Male(66.7%)	Age, (years) 60.1±10.2 Age (years) 59.7±10.6 Age (years) 58.5±9.6
PASEO [133]	2009	BMS (n = 90) PES (n =90)	Male(71.1%) Male(68.9%)	Age, (years) 62± 17, Age (years) 63± 15
PASSION [134]	2011	PES(n= 310) BMS (n = 309)	Male(73.9%) Male(78%)	Age, (years) 61±12, Age, (years) 61±13
PRISON[135]	2012	BMS(n=100) SES (n=100)	Male (76%) Male(83%)	Age (years) 59.3±10.2 Age (years) 59.6±10.6
PROTECT [136]	2012	EES (n=4357) SES (n=4352)	Male(77%) Male (76%)	Age (years) 62·3 ±10·6, Age (years) 62·1± 10·7
PROSIT [137]	2011	SES (n = 154) PES (n = 154)	Male(76%) Male(76.6%)	Age (years), 60 .6 ±11, Age (years), 60. 6 ±12
PURICEL [138]	2013	ERL(n= 200) BES(n= 200)	Male(75.5%) Male(73%)	Age (years) 65.9±11.2 Age (years) 64.9±10.
RAVEL [139]	2007	SES(n= 120) BMS (n=118)	Male(70%/) Male(81%)	Age (years) 61.8±10.7 Age (years) 59.7±10.1
RESOLUTE[140]	2011	RESOLUTE - ZES(N=1140) EES(N=1152)	Male(76.7%) Male(77.2%)	Age (years) 64·4 ± 10·9, Age (years) 64·2 ± 10·8

SCOPRIUS[141]	2012	SES (n = 95) BMS (n = 95)	Male(66%) Male(62%)	Age (years) 66 ± 9, Age (years) 66 ± 10
SEASIDE [142]	2011	SES (n= 75) ERL (n= 75)	Male(75%) Male(85%)	Age, (years) 64±10
SESAMI[143]	2011	SES(n=155) BMS (n=155)	Male(82%) Male(81%)	Age, (years) 63±15, Age (years) 63± 19
SIRTAX [144]	2008	SES(n= 503) PES (n = 509)	Males (69.4%) Male(72.0%) Male (79.8%)	Age (years) 62 ± 10
SORT OUT III 18 MONTHS [145]	2010	ZES (n = 1,162) SES (n =1,170)	Male(73%) Male(74%)	Age(years), 64.3± 10.7 Age (years), 64.3± 10.8
SORT OUT III[146]	2012	ZES (n = 1,162) SES (n = 1,170)	Male(73%) Male(74%)	Age, (years) 64.3± 10.7, Age (years) 64.3±10.8
SORT OUT IV [147]	2012	EES (n=1390), SES (n=1384),	Male(75.9%) Male(75.2%)	Age years , 64.2 ±10.9, Age years, 64.0±10.8
SPIRIT II 3 YEARS [148]	2009	EES (n = 223) PES (n = 77)	Male(71%) Male(79%)	Age (years) 62±10, Age (years) 62±9
TAXI LATE [149]	2007	SES(n= 100) PES (n= 102)	Male(77%), Male(83%)	Age (years), 65. 6±10, Age (years) ,63. 6± 10
TAXUS [150]	2011	BMS (n=1397) PES (n=1400)	Age (81,7%) Age (71.5%)	Age (years), 62.2±10.7 Age (years), 62.8±11.0
TAXUS IV[151]	2009	BMS (n=643) PES (n = 651	Male (72.2%) Male(71.7%)	Age (years) 62.1±11.0 Age (years)

				62.8±11.2
TAXUS VI[152]	2009	BMS (n=233) PES(n =217)	Male (70.2%), Male (68.7%)	Age (years) 62.9 ± 11.2, Age, (years) 62.8 ±10.8,
TWENTE[153]	2013	Resolute- ZES (n= 697) EES(n= 694)	Men (72.5%) Men (72.6%)	Age (years) 63.9 ± 10.9, Age (years) 64.5 ± 10.7
Typhoon[154]	2011	SES (n=355) BMS (n=357)	Male (77.7%) Male(78.6%)	Age, (years) 59.3±13.2 Age, (years) 59.2±11.7,
ZOMAXX[155]	2013	ZES (n=199) PES (n=197)	Male (75%) Male(77%)	Age (years) 63 ± 10 Age (years) 63 ± 11